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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,273	06/27/2005	Kostas Kosmatopoulos	260449US0XPCT	5023
22850	7590	07/10/2008		
OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C. 1940 DUKE STREET ALEXANDRIA, VA 22314			EXAMINER BRISTOL, LYNN ANNE	
			ART UNIT	PAPER NUMBER
			1643	
			NOTIFICATION DATE	DELIVERY MODE
			07/10/2008	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com  
oblonpat@oblon.com  
jgardner@oblon.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/511,273	<b>Applicant(s)</b> KOSMATOPOULOS ET AL.	
	<b>Examiner</b> LYNN BRISTOL	<b>Art Unit</b> 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 15 February 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 7 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 7 is/are rejected.
- 7) ☒ Claim(s) 4 and 5 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/15/08</u> .   | 6) <input type="checkbox"/> Other: _____                          |

**DETAILED ACTION**

1. Claims 1-5 and 7 are all the pending claims for this application.
2. Claims 8 and 9 were cancelled by amendment in the Response of 2/15/08.
3. Claims 1-5 and 7 are all the pending claims under examination on the merits.
4. This action is FINAL.

**Withdrawal of Objections**

***Claim Objections***

5. The objection to Claim 9 for reciting the term “antigenes” instead of “antigens” is withdrawn and moot for the cancelled claim.

**Withdrawal of Rejections**

***Claim Rejections - 35 USC § 112, second paragraph***

6. The rejection of Claims 8 and 9 for the recitation “derived” in the phrase “other immunogenic peptide(s) derived from one or more other antigens” (Claim 8) and “another immunogenic peptide derived from...one or more other antigens” (Claim 9) is withdrawn and moot for the cancelled claims.

***Claim Rejections - 35 USC § 112, first paragraph***

***Written Description***

7. The rejection of Claims 8 and 9 under 35 U.S.C. 112, first paragraph for reciting subject matter that is not supported by the original specification (i.e., the claims encompass an undefined genus of derivatives for an undefined genus of “other antigens”) is withdrawn and moot for the cancelled claims.

***Rejections Maintained***

***Claim Rejections- 35 U.S.C. §103(a)***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. The rejection of Claims 1-3 and 7 under 35 U.S.C. 103(a) as being unpatentable over Schirle et al. (J. Immunol. Methods 257:1-16 (2001); cited in the PTO 892 form of 2/22/07) in view of Powell et al. (USPN 20070031882; with priority filing date 2/15/2002; cited on the PTO 892 form of 2/22/07) **as evidenced by** Tatsumi et al. (Can. Res. 63:4481-4489 (8/2003); cited in the PTO 892 form of 10/15/07) and Parker et al. (J. of Immunol. 152:163, 1994; cited in the 892 form of 10/13/06) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 10/15/07 as follows:

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"Schirle discloses HLA-restricted, T-epitope peptides obtained from reverse immunology strategy where predicted HLA- binding peptides are tested in binding and stability assays followed by analysis of in vitro proteasome-mediated digestions of peptides encompassing candidate epitopes. Schirle discloses prediction algorithms for by 20s proteasomes, FRAGPREDICT and PAPROC and additional peptide digest data from the literature. Schirle teaches that the goal of combining proteasomal prediction algorithms with epitope prediction is already possible using combinations of FRAGPREDICT and PAPROC with SYFPEITHI and BIMAS and that more accurate prediction can be based on fully quantified protein digestion data as well as immunoproteasomal digestion data (p. 7, section 2.2). Schirle describes the "reverse immunology" approach as the most successful strategy for the identification of T cell epitopes, and where the strategy can be used to identify peptides from viral or tumor-specific proteins (p. 2, Col. 1, ¶2-3). Schirle appreciates targeting viral- and tumor-associated antigens using the "reverse immunology" method but does not specifically teach EphA2 derived peptides or substituted forms thereof.

Powell discloses the ephrin kinase or EphA2 protein [0012, SEQ ID NO:2], and using immunogenic peptides for B-epitopes in treating HIV/AIDS [0009- 0010; 0183-0185; 0274]. Powell teaches the full length EphrinA2 protein comprising sequences corresponding to SEQ ID NOS: 4, 6, 7 and 8 (see attached sequence search alignment from the Office Action of 2/22/07). Powell does not disclose identifying or using T epitope peptides derived from the EphA2 protein, but appreciates EphA2-derived immunogenic peptides. As evidenced by Tatsumi, HLA-restricted, T-epitope peptides were inherent to the EphA2 protein because Tatsumi isolated immunogenic peptides.

Parker teaches methods (BIMAS program) to identify peptides potentially capable of binding to HLA-A\*0201 and selecting those with CTL-inducing properties. Parker discloses examples of epitopes ranging from antigenic proteins from viruses such as HTLV and HIV and endogenous peptides (Table VII) selected for HLA restriction and CTL-inducing properties for immunotherapy. Parker teaches that it is possible to select and/or generate by substitution immunogenic peptides from normal, endogenously expressed proteins using the BIMAS method that would otherwise be tolerated by T-cells.

One skilled in the art at the time the invention was made would have been motivated to have produced the instant claimed immunogenic peptide and been assured of reasonable success in doing so based on the combined disclosures of Schirle, Powell, Tasumi and Parker because Schirle explicitly teaches the advantages of selecting T-epitope, HLA peptides using the reverse immunology strategy over other methods, Parker discloses dominant anchor residues important in the HLA molecule for selecting T-cell peptide epitopes using the BIMAS program which is also disclosed in Schirle, and Powell discloses using immunogenic EphA2 derived peptides and where Powell was in possession of the entire ephrin A2 protein the T-epitopes were inherent to the EphA2 protein as evidenced by Tatsumi. Parker also provide the motivation to substitute amino acid residues into peptides in order to overcome tolerance, especially for endogenously expressed proteins.

One skilled in the art would have been reasonably assured of success in producing the peptide T-epitopes from the EphA2 protein because the protein sequence for the EphA2 protein was already disclosed by Powell and T-epitopes were inherent to the EphA2 protein as evidenced by Tatsumi, and because Schirle and Parker provide further method support for identifying T-epitopes with the properties of being HLA-restricted and immunogenic for T cells using methods comprising the BIMAS protocol and peptides further being selected by the "reverse immunology" strategy of Schirle having already been successfully isolated.

For all of the foregoing reasons, the claims were prima facie obvious at the time the invention was made over Schirle, Powell as evidenced by Tatsumi and Parker."

Applicants' allegations on pp. 4-7 of the Response of 2/15/08 and the 1.132

Declaration of Dr. Kosmatopoulos have been carefully considered but are not found persuasive.

A) Applicants' attorney response essentially summarizes the contents of the 1.132 Declaration, and in both instances, it is alleged that Tatsumi is not an effective art reference against the claimed invention because Tatsumi is published on 8/2003 and

the instant claims obtain benefit of the priority filing date for the PCT/FR03/01280 (4/23/03) and foreign priority to 4/23/02 for FR 02/05048. See p. 4 of the Response and section 4 of the declaration.

#### Examiner's Reply

Tatsumi is effective as art to show inherency for T-cell epitopes in the EphA2 protein pursuant to MPEP 2131.01:

"III. To show that a characteristic not disclosed in the reference is inherent"...Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO, Inc.* 190 F3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999)...Also note that the critical date of extrinsic evidence showing a universal fact *need not antedate* the filing date (MPEP 2124)."

Other than challenging the Tatsumi reference for its publication date, the relevancy and/or substance of the reference has not been addressed by attorney arguments or by Dr. Kosmatopoulos as to whether the citation is improper.

*Thus, effectively, the response to this 103 rejection is incomplete.*

B) Applicants' attorney arguments and the Declaration of Dr. Kosmatopoulos discuss each of the individual references and conclude in section 12 of the declaration that "the skilled artisan would not have found any motivation in the Schirle proteasomal cleavage algorithms, nor in Powell's B-cell epitopes, to determine if EphA2 contains T-

epitopes. No information is given in Parker about how to identify a T-epitope produced by proteosome cleavage from a pool of high affinity peptides, and the skilled artisan was not assured of reasonable success by using prediction algorithms for proteasomal cleavage as exposed by Schirle.”

#### Examiner’s Reply

The examiner submits that none of the claimed peptides are so much as limited as to their affinity, thus the basis of Applicants argument, that at most, only high affinity peptides could even be expected from the method of Schirle is wholly misplaced and irrelevant. Further, in the absence of considering the Tatsumi disclosure, the arguments of counsel and Dr. Kosmatopoulos essentially preclude there being any possibility of an endogenous T-cell epitope anywhere in the EphA2 structure based on the disclosures of Schirle, Powell and Parker. Tatsumi is *dispositive* to the presumption that T-cell epitopes would not be expected in the EphA2 structure. Finally, as between the methods disclosed in Schirle, Powell and Parker, Applicants have not shown that any other methods were available at the time of the invention that could have been used to identify T-cell epitopes. Thus, the skilled artisan at the time of the invention had at their disposal the art recognized techniques disclosed in Schirle, Powell and Parker for identifying immunogenic peptide epitopes.

Under the recent KSR decision, the cited references of art are not required to “*explicitly* teach or suggest” all of the steps in achieving a product-based outcome. The Supreme Court has determined in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. \_\_, 82, USPQ2d 1385 (2007), that “a person of ordinary skill attempting to solve a problem will”

not “ be led only to those elements of prior art designed to solve the same problem.....” (KSR, 550 U.S. at\_, 82 USPQ2d at 1397). In addition, the court found that “When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability” (KSR, 550 U.S. at\_, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding “that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'” (KSR, 550 U.S. at\_, 82 USPQ2d at 1397) and has further determined that “.....[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results” (KSR, 550 U.S. at\_, 82 USPQ2d at 1395). The court further found that “..... the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious” (KSR, 550 U.S. at\_, 82 USPQ2d at 1395-1396). Thus, when considering obviousness of a combination of known elements, the operative question is “whether the improvement is more than the predictable use of prior art elements according to their established functions” ((KSR, 550 U.S. at\_, 82 USPQ2d at 1396).

For the reasons set forth in the Office Action 10/15/07 and as set forth hereinabove, the rejection of the peptide invention is maintained over Schirle in view of

Powell **as evidenced by** Tatsumi and Parker.

### ***Conclusion***

9. No claims are allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/  
Primary Examiner, Art Unit 1643